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The furosemide stress test predicts successful discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury

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ABSTRACT

Purpose: There is still no good method for predicting renal recovery and successful discontinuation of continuous renal replacement therapy (CRRT). This study assessed the ability of the furosemide stress test (FST) to predict successful discontinuation of CRRT.

Materials and methods: This prospective single-center study included patients with acute kidney injury who underwent an initial attempt at discontinuation of CRRT. Successful discontinuation was defined as alive without renal replacement therapy for 7 days after discontinuation. Furosemide 1.0 mg/kg was administered intravenously within 2 h after discontinuation of CRRT. Urine output was recorded for the next 2 h. Receiver-operating characteristic curve and logistic regression analyses were performed to determine the best discriminative variable and to identify independent risk factors.

Results: Discontinuation of CRRT was successful in 30 of 55 patients. The area under the curve for prediction of successful discontinuation was significantly greater for urine output in the 2 h following the FST (0.913) than for 24-h urine output on the previous day (0.739, $P = 0.003$) and urine neutrophil gelatinase-associated lipocalin (0.725, $P = 0.020$). A 2-h urine output of 188 mL had optimal sensitivity (0.800) and specificity (0.920). Multivariate analysis showed that 2-h urine output independently predicted successful discontinuation.

Conclusions: A urine output >188 mL in the first 2 h after FST predicted successful discontinuation of CRRT.

1. Introduction

Acute kidney injury (AKI) is a common complication in critically ill patients [1]. More than 20 % of patients with AKI in the intensive care unit (ICU) receive renal replacement therapy (RRT), the majority of which is continuous renal replacement therapy (CRRT), within the first week of their ICU stay [2,3]. However, despite being an important measure for rescuing patients with severe AKI, CRRT does not come without problems. Associated difficulties include catheter-related bloodstream infection, thrombosis, bleeding, hemodynamic instability, and even interference with recovery of renal function [4]. Therefore, CRRT should be discontinued as soon as possible after renal function is restored. As with the timing of its initiation, recognizing when to stop CRRT may be challenging, and renal function is difficult to evaluate during CRRT [5,6]. Without standards for discontinuation, the failure rates have ranged widely from 34 % to 79 % [2,7–9]. Observational studies have shown that the most significant predictor of successful discontinuation of CRRT is urine production, although this is affected by use of diuretics [2]. Other studies have demonstrated that the furosemide-induced diuretic response after cessation of CRRT is useful for prediction of renal recovery during the hospital stay [10,11]. Van der Voort et al. found that a high 4-h urine output in the 24 h following intravenous administration of furosemide 0.5 mg/kg/h for 24 h after termination of CRRT predicted renal recovery during the hospital stay [11,12]. However, the doses of diuretics administered in these studies were variable and the urine output thresholds were not consistent.

In recent years, the furosemide stress test (FST) has been confirmed to be useful for predicting development of stage 3 AKI [13–17], and it

Abbreviations: AKI, Acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; AUC, Area under the curve; CI, Confidence interval; CRRT, Continuous renal replacement therapy; FST, Furosemide stress test; ICU, Intensive care unit; IQR, Interquartile range; NGAL, Neutrophil gelatinase-associated lipocalin; ROC, Receiver-operating characteristic; RRT, Renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

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would be useful to know whether the FST could also predict recovery of renal function after CRRT and successful discontinuation of this therapy.

The aim of this study was to determine if the FST can identify whether or not CRRT can be successfully discontinued. We hypothesized that the urine output in the 2 h following intravenous administration of furosemide 1.0 mg/kg could predict the likelihood of discontinuation of CRRT being successful.

2. Materials and methods

2.1. Patients

This prospective single-center study was performed between January 2020 and July 2023 in a mixed ICU at Zhejiang Hospital, a tertiary teaching institution in China. The study protocol was approved by the Zhejiang Hospital ethics committee (approval number 201935 K). Informed consent was obtained for each study participant or their legal representative.

All patients aged 18 years or older with AKI in whom a first attempt at discontinuation of CRRT was planned were screened for eligibility. AKI was defined and staged according to the 2012 KDIGO guidelines [18]. The following exclusion criteria were applied: preexisting end-stage renal disease (i.e., stage 5 chronic kidney disease); history of renal transplantation; pregnancy; abandonment of CRRT or other life support therapy; CRRT administered for <24 h; furosemide allergy; and active volume expansion after discontinuation of CRRT.

2.2. Study protocol

The decision to attempt discontinuation of CRRT was made by the treating team if the patient's systemic condition was stable, as indicated by improvement in volume overload, stabilization of the electrolyte and acid-base balance, hemodynamic stability, and increased urine output.

Furosemide 1.0 mg/kg was administered as an intravenous bolus within 2 h of stopping CRRT. Urine output was recorded for 2 h after administration of furosemide. The treating team decided whether to replace the urinary loss with isotonic intravenous fluid according to the patient's volume status. We considered CRRT to be discontinued when it had been stopped for ≥12 h [7]; otherwise, the case would be excluded until a CRRT cessation time of ≥12 h had been reached. The decision to re-initiate RRT was made by the treating team.

Demographic data and clinical information were collected at the time of admission to the ICU and included the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores and the requirement for mechanical ventilation and vasopressors. Data on physiological and laboratory variables, including mean arterial pressure, urine output, fluid balance, urine neutrophil gelatinase-associated lipocalin (NGAL), serum creatinine, blood urea nitrogen, blood gas analysis, complete blood count, and C-reactive protein, were collected at the time of initiation and discontinuation of CRRT. Successful discontinuation was defined as alive and free from RRT for 7 days after initial discontinuation [2].

2.3. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation if they were normally distributed or as the median (interquartile range [IQR]) if not. Categorical variables are shown as the number (percentage). Continuous variables were compared between groups using the *t*-test if normally distributed and the Mann–Whitney *U* test if not normally distributed. Categorical variables were compared between groups using the chi-squared test. The ability of various parameters to predict successful discontinuation of CRRT was assessed by receiver-operating characteristic (ROC) curve analysis. The Youden index was calculated to determine the optimal cut-off value that discriminated successful discontinuation of CRRT. The area under the curve (AUC) for each parameter of interest was compared using the Delong test. Multivariate logistic regression analysis was performed to identify independent predictors of successful discontinuation of CRRT using variables that had a *P*-value of <0.05 in univariate analysis. The statistical analyses were performed using SPSS software (version 29.0; IBM Corp., Armonk, NY, USA). All statistical tests were two-tailed, and a P-value <0.05 was considered statistically significant.

3. Results

3.1. Study population and outcome

Forty-seven of the 119 patients who received CRRT during the study period died during CRRT, two were transferred out of the ICU during CRRT, three withdrew consent to treatment, and four were identified as having preexisting end-stage renal disease. Among the remaining 63 patients in whom an initial attempt at discontinuation of CRRT was made, two received CRRT for <24 h, four withdrew consent to treatment, and two required active volume expansion (Fig. 1). Finally, the study included 55 patients, 65.6 % of whom were male. The mean age was 76.6 years. There were 30 cases in the successful discontinuation group and 25 in the unsuccessful discontinuation group. The median time to re-initiation of RRT in patients in whom the initial attempt at discontinuation was unsuccessful was 43.3 h (IQR 19.2–81.4). In all cases, the main reason for re-initiation of CRRT was oliguria. Other reasons were clinical perception of volume overload ($n = 11$), high serum creatinine ($n = 4$), and hyperkalemia ($n = 2$). The 28-day survival rate was higher in the successful group than in the unsuccessful group (83.3 % vs. 76.0 %); however, the between-group difference was not statistically significant ($P = 0.498$). The 90-day survival rate also tended to be higher in the successful group than in the unsuccessful group, but the difference was more pronounced (70.0 % vs. 44.0 %, $P = 0.052$). Among survivors, the 28-day RRT dependency rate was significantly lower in the successful group 0.0 % vs. 68.4 %, $P < 0.001$), as was the 90-day RRT dependence rate (8.7 % vs. 50.0 %, $P = 0.014$).

3.2. Patient characteristics at time of ICU admission and initiation of CRRT

There was no statistically significant between-group difference in baseline characteristics at the time of ICU admission ($P > 0.05$) (Table 1). At the time of initiation of CRRT, there were more patients with sepsis-associated AKI in the unsuccessful group than in the successful group (76.0 % vs. 46.7 %, $P = 0.027$). The unsuccessful group tended to have a higher C-reactive protein level at the time of initiation of CRRT, but the difference did not reach statistical significance ($P > 0.05$). Furthermore, there was no statistically significant between-group difference in AKI stage, SOFA score, serum creatinine, or fluid accumulation during the interval between admission to the ICU and initiation of CRRT (P > 0.05) (Table 2).

3.3. Clinical characteristics at time of discontinuation of CRRT

At the time of discontinuation of CRRT, the median 24-h urine output on the previous day had been significantly higher in the successful group than in the unsuccessful group (670 mL [IQR 357–887] vs 200 ml [IQR 100–525], $P = 0.002$). The median urine NGAL level was 587.20 ng/mL (IQR 159.45–999.45) in the successful group and 1235.25 ng/mL (IQR 527.05, 3000.00) in the unsuccessful group ($P = 0.020$). Median urine output in the 2 h after the FST was significantly greater in the successful group (285 mL [IQR 199–382] vs 70 mL [IQR 38–135], $P < 0.001$). There was no significant difference in the APACHE II or SOFA score, blood lactic acid level, blood creatinine, duration of CRRT, or the cumulative fluid balance between the two groups at the time of discontinuation of CRRT ($P > 0.05$) (Table 3).

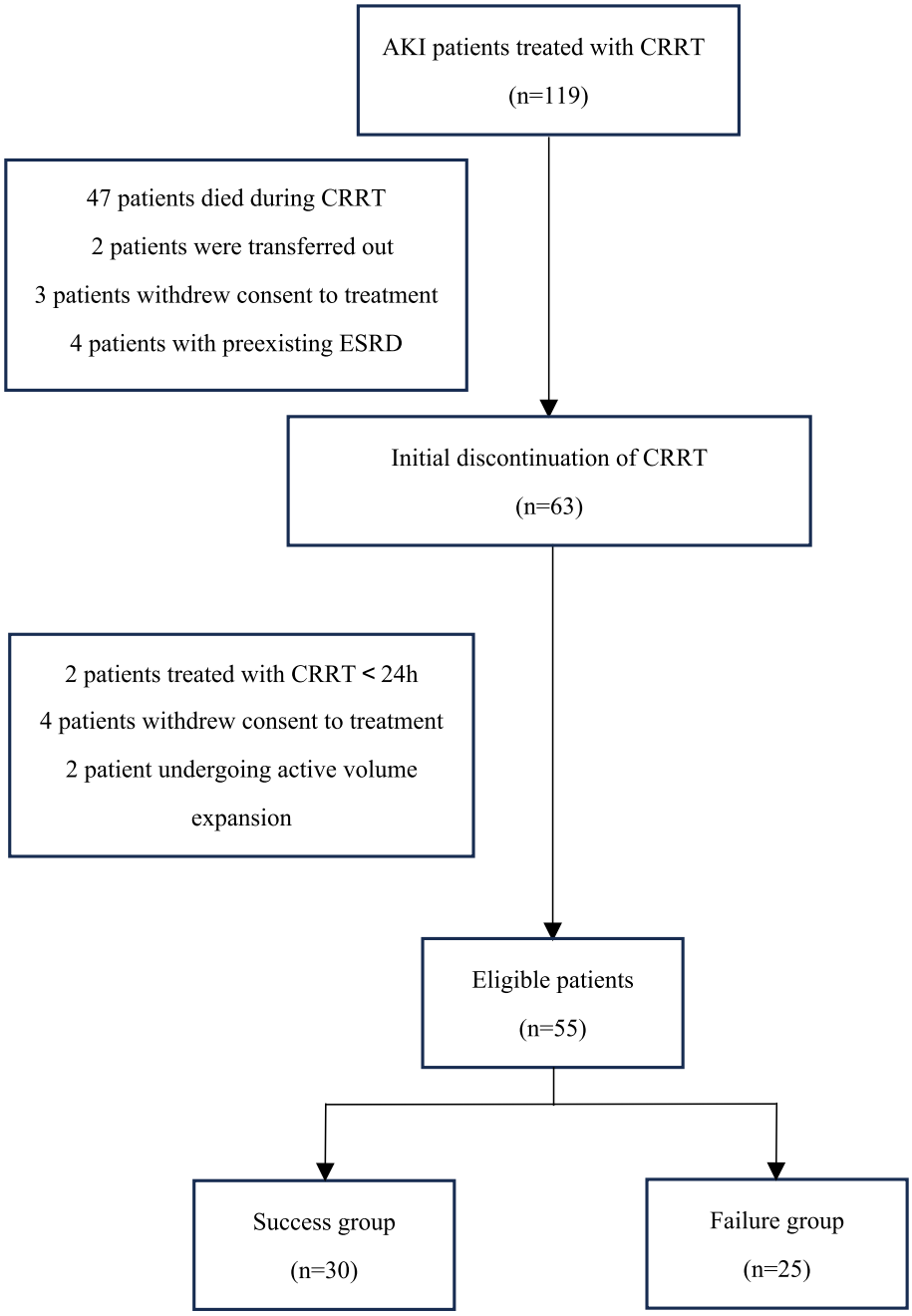

Fig. 1. The flow chart of patient enrollment. AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ESRD, end-stage-renal-disease.

3.4. ROC curve and multivariate analyses

ROC curve analysis showed that the AUC for prediction of successful discontinuation of CRRT was 0.913 (95 % confidence interval [CI] 0.840–0.986) for urine output in the 2 h after the FST (Fig. 2A). A 2-h urine output of 188 mL had optimal sensitivity (0.800 [95 % CI 0.648–0.952]) and specificity (0.920 [95 % CI 0.806–1.000]). The respective AUCs for 24-h urine output and urine NGAL for prediction of successful discontinuation of CRRT were 0.739 (95 % CI 0.605–0.872) and 0.725 (95 % CI 0.586–0.864) (Fig. 2B, C). The AUC for urine output in the 2 h after the FST was significantly greater than the AUC for 24-h urine output on the previous day ($P = 0.003$) and that for urine NGAL ($P = 0.020$). Although 24-h urine output on the previous day had slightly higher sensitivity, among the three variables, the specificity and positive and negative predictive values were highest for urine output in the 2 h after the FST (Table 4). We then evaluated the predictive performance of a combination of the cutoff values for 2-h urine output after FST and urine NGAL. Compared with a 2-h urine output of >188 mL after FST alone, the combination of a 2-h urine output of >188 mL after FST or a urine NGAL level < 731 ng/mL had better sensitivity (0.862 [95 % CI 0.729–0.996]) and specificity (0.923 [95 % CI 0.813–1.000]) as well as a better positive predictive value (0.926 [95 % CI 0.820–1.000]) and negative predictive value (0.857 [95 % CI 0.719–0.995]).

Multivariate analysis that included AKI with sepsis, urine output in the 2 h following the FST, 24-h urine output on the day before discontinuation, and urine NGAL before discontinuation identified the 2-h urine output after the FST to be the only independent predictor of successful discontinuation of CRRT (odds ratio 8.870 for each 100-mL increase in urine output, 95 % CI 2.363–33.301, $P = 0.001$; Table 5). The AUC for the final model that included the above four variables was 0.940

Table 1
Baseline characteristics at ICU admission.

Variables	Overall (n = 55)	Success group (n = 30)	Failure group (n = 25)	p
Age, years	76.6 ± 14.2	73.8 ± 15.2	79.9 ± 12.5	0.115
Male, %	36 (65.6)	18 (60.0)	18 (72.0)	0.351
Body weight, kg	60 (55–70)	60 (51–68)	65 (60–72)	0.081
Comorbidities (n, %)				
Chronic kidney disease*	14 (25.5)	7 (23.3)	7 (28.0)	0.692
Hypertension	36 (65.5)	18 (60.0)	18 (72.0)	0.351
Diabetes	26 (47.3)	13 (43.3)	13 (52.0)	0.522
Chronic heart failure	13 (23.6)	9 (30.0)	4 (16.0)	0.224
Malignancy	8 (14.5)	3 (10.0)	5 (20.0)	0.446
Indication for ICU admission				
Respiratory failure	22 (40.0)	12 (40.0)	10 (40.0)	0.438
Heart failure	8 (14.5)	6 (20.0)	2 (8.0)	
Sepsis	9 (16.4)	4 (13.3)	5 (20.0)	
Post-operative	5 (9.1)	4 (13.3)	1 (4.0)	
Trauma	7 (12.7)	3 (10.0)	4 (16.0)	
Others	4 (7.3)	1 (3.3)	3 (12.0)	
Apache II score	25.2 ± 7.4	25.0 ± 7.9	25.4 ± 6.8	0.831
SOFA score	9.0 (7.0–11.0)	9.5 (8.0–12.0)	8.0 (6.0–10.5)	0.164
Vasopressors support (n, %)	27 (49.1)	18 (60.0)	9 (36.0)	0.076
Mechanical ventilation (n, %)	37 (67.2)	21 (70.0)	16 (64.0)	0.637

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment. * 15 mL/min ≤ eGFR <60 mL/min.

(95 % CI 0.882–0.998; Fig. 3), which was slightly greater than that for the 2-h urine output after the FST (P = 0.272). There were no FST-related adverse events.

4. Discussion

In this prospective study, we found that the 2-h urine output after the FST was an independent predictor of discontinuation of CRRT. At the optimal cut-off value of 188 mL, the AUC for the 2-h urine output after the FST that predicted successful discontinuation was 0.913, which was better than the AUCs for 24-h urine output on the previous day and the urine NGAL level before discontinuation. A 2-h urine output >188 mL after the FST was better able to predict successful discontinuation of CRRT when combined with a urine NGAL level of <731 ng/mL than when used alone. Although AKI with sepsis, 24-h urine output, and urine NGAL were not independent predictors of successful discontinuation of CRRT, combining the above metrics may improve the discriminatory ability of the model further.

In recent years, there has been a gradual increase in the number of studies on the timing of discontinuation of CRRT [19,20]. Although a few studies have reported that creatinine clearance [21], urinary creatinine concentration [22], serum cystatin C, and NGAL [23] may predict successful discontinuation of CRRT, other studies have shown that urine output is still the most important factor [2,10,24]. Raurich et al. [25] reported that the area under the ROC curve for prediction of a successful CRRT weaning test was higher for the 6-h urine output after discontinuation of CRRT. Heise et al. [26] found that 8-h urinary output after cessation of CRRT was one of three parameters that independently influenced the recovery of kidney function during CRRT-free intervals. However, the various studies have shown considerable variation in urine output in their successful CRRT discontinuation groups [2,10,24]. Furthermore, it was difficult to determine a threshold for urine output in retrospective studies because of the use of diuretics. Uchino et al. [2] concluded that the ability of urine output to predict successful discontinuation of CRRT was negatively affected by diuretic use.

Although use of diuretics reduces the comparability of urine output between patients, these agents are valuable in terms of being able to discontinue CRRT. Although assessment of recovery of renal function in patients on CRRT is often difficult, furosemide is a good tool for examination of the integrity of the renal tubules and reserve. Provided that the renal tubules are intact, loop diuretics, especially furosemide, reduce sodium reabsorption in the thick ascending limb of the loop of Henle, resulting in increased urinary sodium and water excretion [27]. Therefore, recovery of the renal response to furosemide in patients on CRRT implies recovery of function of the renal tubules. It has been confirmed that the furosemide-induced diuretic response in patients without immediate recovery of renal function within 24 h after cessation of CRRT is of additional value in terms of prediction of eventual renal recovery during the hospital stay [11]. The retrospective study by Raurich et al. [25], in which patients received diuretics at various dosages and via different routes, still found that the area under the ROC curve for 6-h urine output was better able to predict weaning from CRRT in patients who received furosemide than in those who did not (0.94 vs. 0.85).

Table 2
Characteristics at CRRT initiation.

Variables	Overall (n = 55)	Success group (n = 30)	Failure group (n = 25)	p
AKI stage (n,%)				
Stage 1	4 (7.3)	3 (10.0)	1 (4.0)	0.684
Stage 2	8 (14.5)	4 (13.3)	4 (16.0)	
Stage 3	43 (78.2)	23 (76.7)	20 (80.0)	
Contributing factors to AKI				
Sepsis	33 (60.0)	14 (46.7)	19 (76.0)	0.027
Low cardiac output	16 (29.1)	8 (26.7)	8 (32.0)	0.665
Hypovolemia	8 (14.5)	5 (16.7)	3 (12.0)	0.462
Major surgery	4 (7.3)	4 (13.3)	0 (0)	0.117
Other	4 (7.3)	4 (13.3)	0 (0)	0.117
Apache II score	26.2 ± 7.6	26.3 ± 8.5	26.0 ± 6.7	0.921
SOFA score	10.0 (8.0–12.0)	10.0 (9.0–13.0)	10.0 (7.0–11.0)	0.054
Vasopressors support (n, %)	34 (61.8)	22 (73.3)	12 (48.0)	0.054
mechanical ventilation (n, %)	41 (74.5)	25 (83.3)	16 (64.0)	0.101
MAP, mmHg	84 ± 15	85 ± 16	83 ± 14	0.669
pH	7.32 ± 0.09	7.33 ± 0.10	7.32 ± 0.09	0.788
Blood lactate (mmol/L)	1.90 (1.19–4.85)	2.10 (1.35–5.62)	1.57 (1.11–2.95)	0.204
PaO_2/FiO_2	247 ± 100	230 ± 107	268 ± 89	0.172
Serum creatinine (μmol/L)	264.7 (187.9–395.0)	241.0 (173.3–383.7)	304.0 (204.2–460.3)	0.187
Blood urea nitrogen (mmol/L)	27.62 ± 15.14	27.38 ± 16.78	27.91 ± 13.24	0.899
Albumin (g/L)	30.65 ± 4.96	31.15 ± 5.85	30.14 ± 3.97	0.516
Leukocyte count (*10^9/L)	8.59 (6.39–15.28)	8.69 (6.47–15.99)	8.15 (6.25–14.09)	0.892
Hemoglobin (g/L)	86 (71–108)	87 (70–116)	86 (73–107)	0.780
Platelet count (*10^9/L)	121 ± 63	128 ± 66	113 ± 59	0.374
C-reactive protein (mg/dL)	80.77 (43.17–127.63)	64.56 (23.09–112.56)	94.76 (51.27–186.69)	0.053
Fluid accumulation between ICU admission and CRRT initiation (mL)	1490 (220–2363)	1500 (210–2450)	1481 (223–2357)	0.815

CRRT, continuous renal replacement therapy; AKI, acute kidney injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MAP, Mean arterial pressure.

Table 3
Characteristics at CRRT discontinuation.

Variables	Overall ($n = 55$)	Success group ($n = 30$)	Failure group ($n = 25$)	P
Apache II score	19.5 ± 5.5	18.6 ± 5.7	20.6 ± 5.1	0.165
SOFA score	8.0 (6.0–10.0)	8.0 (6.7–10.3)	8.0 (6.0–10.5)	0.651
Vasopressors support (n, %)	20 (36.4)	12 (40.0)	8 (32.0)	0.539
Mechanical ventilation (n, %)	33 (60.0)	20 (66.7)	13 (52.0)	0.269
MAP, mmHg	85 ± 13	83 ± 15	87 ± 10	0.322
pH	7.43 ± 0.06	7.45 ± 0.06	7.42 ± 0.07	0.105
Blood lactate (mmol/L)	1.30 (1.00–2.00)	1.50 (0.89–2.33)	1.22 (1.05–1.55)	0.207
PaO_2/FiO_2	281 (228–360)	270 ()221–393	286 (240–350)	0.716
Serum creatinine (μmol/L)	106.5 (59.0–159.0)	85.0 (54.5–137.6)	122.5 (63.0–179.5)	0.233
Urine NGAL (ng/mL)	785.45 (387.55–2963.70)	587.20 (159.45–999.45)	1235.25 (527.05–3000.00)	0.020
Blood urea nitrogen (mmol/L)	7.38 (5.30–11.59)	7.30 (5.09–10.77)	7.38 (5.68–12.65)	0.521
Albumin (g/L)	32.30 ± 4.31	32.78 ± 4.39	31.78 ± 4.25	0.429
Leukocyte count ($*10^9$/L)	8.20 (5.93–11.87)	9.58 (5.87–12.57)	7.85 (6.00–9.92)	0.452
Hemoglobin (g/L)	85 ± 20	86 ± 22	85 ± 18	0.860
Platelet count ($*10^9$/L)	85 (52–139)	79 (54–121)	97 (50–157)	0.554
C-reactive protein (mg/dL)	99.7 ± 66.3	97.1 ± 65.6	102.9 ± 68.5	0.747
CRRT duration (hours)	84.7 (65.7–166.8)	86.1 (48.8–176.6)	81.2 (66.0–156.0)	0.695
Cumulative fluid balance from CRRT initiation to CRRT discontinuation (mL)	−1634 ± 3991	−1013 ± 4295	−2354 ± 3555	0.222
24-h urine output on the previous day (mL)	400 (180–750)	670 (357–887)	200 (100–525)	0.002
2-h urine output after FST(mL)	175 (70–300)	285 (199–382)	70 (38–135)	<0.001

CRRT, continuous renal replacement therapy; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; MAP, Mean arterial pressure; NGAL, neutrophil gelatinase-associated lipocalin; FST, furosemide stress test.

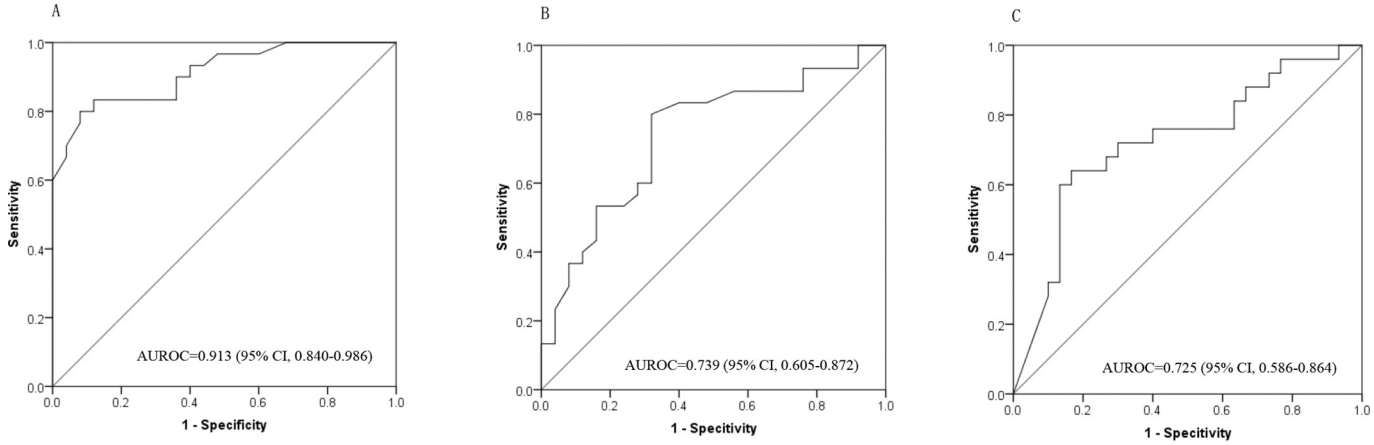

Fig. 2. ROC curves of 2-h urine output after FST (A), 24-h urine output on the previous day (B) and urine NGAL before discontinuation (C) for the prediction of successful discontinuation of CRRT.

Table 4
Diagnostic test parameters for 2-h urine output after FST, 24-h urine output on the previous day and urine NGAL.

	2-h urine output after FST	24-h urine output on the previous day	urine NGAL
AUC (95 %CI)	0.913 (0.840–0.986)	0.739 (0.605–0.872)	0.725 (0.586–0.864)
Sensitivity (95 % CI)	0.800 (0.648–0.952)	0.828 (0.681–0.974)	0.625 (0.416–0.834)
Specificity (95 % CI)	0.920 (0.806–1.000)	0.680 (0.483–0.877)	0.714 (0.504–0.925)
Positive predictive value (95 %CI)	0.923 (0.813–1.000)	0.750 (0.591–0.909)	0.714 (0.504–0.925)
Negative predictive value (95 %CI)	0.793 (0.636–0.950)	0.772 (0.583–0.963)	0.625 (0.416–0.834)
Cut-off	188 mL	325 mL	731 ng/mL

FST, furosemide stress test; NGAL, neutrophil gelatinase-associated lipocalin; AUC, area under the curve.

Table 5
Multivariate logistic regression analysis for successful discontinuation of CRRT.

	β coefficient	Odds Ratio	95 % CI	P
AKI with sepsis	−1.649	0.192	0.028–1.321	0.094
2-h urine output after FST, 100 mL	2.183	8.870	2.363–33.301	0.001
24-h urine output on the previous day, 100 mL	0.002	1.002	0.806–1.247	0.982
Urine NGAL, ng/mL	−0.001	0.999	0.999–1.000	0.186

CRRT, continuous renal replacement therapy; FST, furosemide stress test; NGAL, neutrophil gelatinase-associated lipocalin.

A standardized weight-based furosemide dose for the FST was first described in 2013 [13]. Subsequent studies have confirmed that the FST can predict whether patients with AKI will progress to stage 3, which may also assist in determining the timing of initiation of CRRT [14–17]. Some investigators have recently suggested that apart from predicting which patients will develop AKI based on the renal response to furosemide, this concept could also potentially be used to predict recovery of renal function after CRRT in critically ill patients with AKI [12,25].

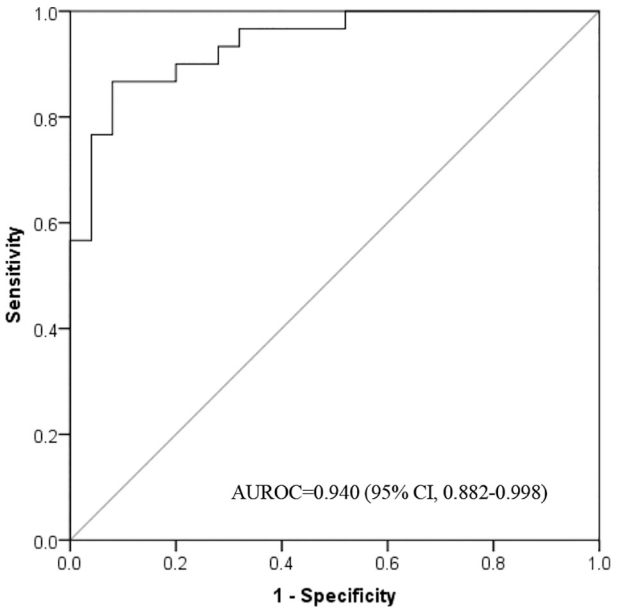

Fig. 3. ROC curve for the final prediction model.

Studies by Van der Voort et al. compared the effect of continuous infusion of furosemide on the recovery of renal function with that of placebo and found that in patients who received furosemide 0.5 mg/kg/h intravenously for 24 h after termination of CRRT, a high 4-h urine output 24 h later predicted renal recovery during the hospital stay with an area under the ROC of 0.84 [11,12]. However, although those authors referred to use of the FST, collecting 4-h urine output after 24 h of continuous infusion of furosemide is clearly different from the currently accepted FST method, and the sample size used for the ROC analysis was only 25. Our study is the first to report on use of the standardized FST to predict weaning from CRRT and confirms its role in predicting successful discontinuation. Furthermore, the results could be predicted 24 h earlier in our study than in the previous study by Van der Voort et al. [12]. Noteworthy in our study is that the FST 2-h urine output threshold for prediction of successful discontinuation was 188 mL, which was in good agreement with the threshold of 200 mL previously reported for prediction of progression of AKI [17].

Novel biomarkers, such as NGAL used to detect early AKI, have also been reported to be associated with renal recovery and predict successful liberation from RRT [28,29]. In a study by Xiaohan et al. [30], serum NGAL was even comparable to urine output for predicting successful CRRT discontinuation in nonseptic AKI patients. However, in our study, the AUC for prediction of successful discontinuation was significantly greater for the 2-h urine output after the FST than for urine NGAL. Since the combination of the two variables had stronger ability in predicting, a joint application of them may be a wise choice. Recent studies of the outcomes of discontinuation of CRRT have developed predictive models by combining a variety of non-interventional observational indicators, with the majority having an AUC of around 0.80 [7,24,31]. In our study, the AUC for the ability of the FST to predict the outcome was greater than that in most other studies, and 24-h urine output and urine NGAL could improve the value of the model further. One potential clinical application of the findings of this study is that when the purpose of CRRT has been achieved, performing the FST to assess recovery of renal function during each CRRT-free interval for filter replacement, rather than after the decision from clinicians to stop CRRT, may help to allow CRRT to be withdrawn as early as possible. In the future, if the results of the FST can be integrated into a larger CRRT discontinuation outcome prediction model, the predictive power of the model may be improved further.

It should be considered that the duration of AKI and likelihood of successful discontinuation of CRRT are also related to the patient's primary disease and pre-existing renal function. In our study, there was no significant between-group difference in the proportion of patients with CKD, apart from more patients with sepsis in the unsuccessful group. Counterintuitively, patients in the successful group were more likely to be on vasopressors and to have a higher SOFA score at the time of initiation of CRRT. However, the between-group differences in the proportion of patients on vasopressor support and in the SOFA score disappeared at the time of discontinuation of CRRT. In this study, a proportion of patients were on vasopressors at the time of initiation of CRRT even without sepsis, mostly as a result of volume overload or heart failure; however, the overall condition of these patients, including their renal function, might improve more rapidly with the negative fluid balance on CRRT than in their counterparts with severe sepsis.

This study has several limitations. First, it had a single-center design and included a limited number of cases. Second, the decision to discontinue CRRT was made by the treating team without setting consistent criteria for doing so. For example, a patient's volume status might affect their urine output. Third, there were no uniform criteria for re-initiation of CRRT. Although the differences in treatment decisions in the same ICU were relatively small, we cannot exclude the possibility that physicians were inconsistent in determining if and when to restart CRRT and that certain patients in whom this treatment could have been permanently discontinued were restarted on CRRT within 7 days. Fourth, the attending physicians were aware of the results of the FST, which could have been a source of bias. However, because the median delay to re-initiation of CRRT was 43.3 h (IQR 19.2–81.4), subsequent urine output and other conditions were more likely to be the primary factors influencing the physicians' decision to restart RRT rather than urine output after the FST, which was performed within 2 h of stopping CRRT. Finally, we used body weight on admission to determine the furosemide dosage, and the actual weight might have changed after treatment in the ICU, thereby affecting the dosage administered.

In conclusion, a urine output of more than 188 mL in the first 2 h after the FST predicts successful discontinuation of CRRT. This research provides a practical bedside tool for clinical decision-making. Combining the FST with other clinical indicators to build a predictive model for successful discontinuation of CRRT may help us to answer the question of when to discontinue CRRT. The value of the FST in discontinuation of CRRT requires confirmation in larger studies.

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CRediT authorship contribution statement

Liang Xu: Writing – original draft, Methodology, Conceptualization. **Lina Chen:** Investigation, Formal analysis. **Xiangyang Jiang:** Investigation, Data curation. **Weihang Hu:** Validation. **Shijin Gong:** Supervision. **Junjun Fang:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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